XP-002139790

P.D. 15/11/1999
p. 391 a = (1)

PROMOTING STEM CELL ENGRAFTMENT AND PREVENTING GVHD

Abstract# 1733

STUDIES OF MESENCHYMAL STEM CELLS IN NON-HUMAN PRIMATES: EVALUATION OF TOXICITY AND ENGRAFTMENT.

S. M. Devine,[1] A. Bartholomew*,[2] C. Sturgeon*,[2] D. Sher*,[1] S. Weissman*,[1] M. Nelson*,[1] T. Hewett*,[3] T. Chung*,[4] W. Hardy*,[5] S. Moran*,[5] R. Deans*,[5] A. Moseley,[5] N. Mahmud*,[1] R. Hoffman.[1] *[1]Hematology/Oncology; [2]Surgery; [3]Biological Resources Lab; [4]Radiation Oncology, University of Illinois at Chicago, Chicago, IL; [5]Osiris Therapeutics, Inc, Baltimore, MD.*

The bone marrow (BM) contains mesenchymal stem cells (MSC) capable of differentiating along multiple mesenchymal lineages (Science 284:143,1999). Purified populations of MSC have been demonstrated to support hematopoiesis in vitro and may possess the potential to home to the BM and engraft long-term. In order to evaluate the capacity of MSC to engraft and to assess the possibility of adverse events related to the infusion of MSC, we studied the transplantation of either autologous or allogeneic MSC in a baboon model. To date, five juvenile baboons (Papio anubis) have received MSC in two distinct settings. In group 1 (N=3), two animals received lethal irradiation (1,000cGy) followed by autologous (AU) BM and AU MSC retrovirally transduced with enhanced green fluorescent protein (enGFP). A third recipient in that group received only AU enGFP-transduced MSC but no irradiation or BM support. In group 1, there was no toxicity associated with the AU MSC infusion. Transient engraftment of enGFP-transduced MSC was documented on a BM aspirate 14 days following MSC infusion in the non-conditioned animal but none were detected on a day 30 sample. Of the remaining two Group 1 animals, one received an "optimal" dose of BM (> 20 x 10e6/kg CD34+ cells) and MSC (> 20 x 10e6/kg) whereas the other received a "suboptimal" graft of BM (1.0 x 10e6/kg CD34+ cells) and MSC (3.1 x 10e6/kg). The optimal graft recipient recovered both white blood cells (WBC) and platelets (PLT) in < 30 days. Samples of BM were obtained from 1 to 9 months post-transplant and revealed the persistence of gene transduced MSC through 9 months in BM biopsy samples. The suboptimal graft recipient recovered WBC by day 30 but was euthanized due to failure to thrive on day 43. However, enGFP transduced MSC were present on a post-mortem BM biopsy. In Group 2 (N=2), animals received > 2.0 x 10e6/kg PB-derived G-CSF mobilized CD34+ cells and > 20 x 10e6/kg MHC-mismatched(MM) MSC following lethal irradiation. Both recipients recovered WBC (day 10 and 12) and PLT (day 15 and 16) promptly. There were no adverse events related to the infusion of MHC-MM MSC. Specifically, there was no evidence of graft versus host disease(GVHD). Chimerism studies using microsatellite amplification analysis of BM biopsy samples taken prior to day 30 revealed the presence of cells derived from donor MSC. Taken together, these experiments demonstrate that the transplantation of purified populations of either AU or MHC-MM MSC is safe and that MSC are capable of homing to the bone marrow and can establish both short and long-term engraftment. Strikingly, MHC-MM MSC appear capable of engrafting even in the face of significant allogeneic barriers without causing GVHD. This implies that MSC may provide an important new cellular target for gene therapy-based approaches to diseases in man.